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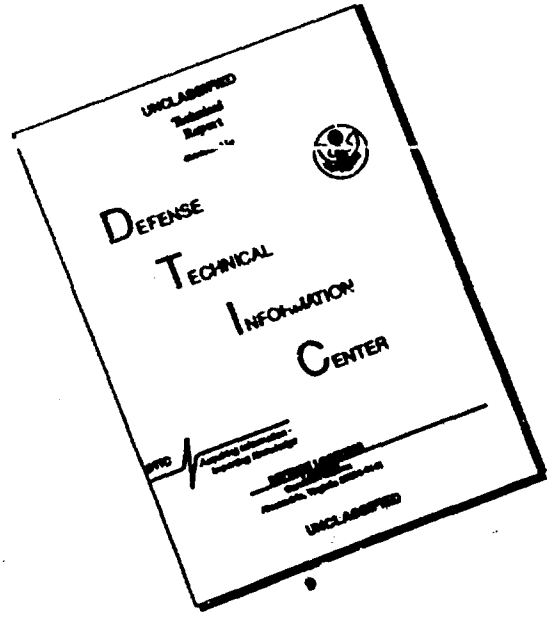

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Evaluation of Biodegradable Cefazolin Sodium Microspheres for the Prevention of Infection in Rabbits with Experimental Open Tibial Fractures Stabilized with Internal Fixation

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Summary: Immediate internal fixation of severe open tibial fractures usually is contraindicated due to the high risk of infection. The objective of this study was to evaluate the efficacy of local antibiotic therapy with biodegradable poly-(DL-lactide-co-glycolide) cefazolin-loaded microspheres for the prevention of infection in experimental open fractures stabilized with internal fixation. Rabbits with experimental tibial fractures that were contaminated with *Staphylococcus aureus* were treated with local application of cefazolin microspheres, an equivalent local dose of free Ancef powder, or systemic Ancef therapy. The bones then were fixed with a four-hole plate, and the animals were observed for 8 weeks. Clinically, deep infection was present in 86% of control animals that received no antibiotics and in 60% of animals that received a 7 day course of systemic Ancef therapy. In contrast, no infections were noted among any of the surviving rabbits that received local therapy with either cefazolin microspheres or free Ancef powder. Significantly higher levels of serum cefazolin were measured at 1 h for animals treated with free Ancef powder (18.7 ± 6.1 μg/ml) than for those treated with cefazolin microspheres (0.57 ± 0.27 μg/ml). Follow-up studies are in progress to evaluate further the potential clinical benefits of local antibiotic therapy for the management of contaminated open fractures in humans.

Despite advances in surgical techniques and the availability of newer antibiotics, infection continues to be a problem in the management of open fractures (8,10,16). Immediate internal fixation of severe (type-III) open fractures (8), especially of the tibial and fibular shafts, is associated with higher rates of infection than other methods of fracture stabilization (3,24,26). Although early internal fixation offers several advantages, including excellent reduction of the fracture, preservation of joint function, and earlier mobility of the patient, it usually is contraindicated due to the high incidence of postoperative complications (3,16). In contrast, the ability to prevent infection may reduce the risks associated with immediate internal fixation and would enable the numerous benefits of this method of fixation to be realized by both the patient and the surgeon.

Because all open fractures are considered to be contaminated at the time of injury, the prevention of

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infection is a primary goal of treatment. In addition to meticulous surgical debridement, parenteral administration of broad-spectrum antibiotics is advocated and remains a cornerstone of therapy (9,18). Systemic antibiotic therapy may be associated with several drawbacks, however, including poor penetration of the antibiotic into ischemic tissue and systemic toxicity; in addition, many patients must be carefully monitored, which necessitates hospitalization (20). This has prompted the search for alternative methods for the delivery of antibiotics into infected soft tissue and bone. Local antibiotic therapy with gentamicin-impregnated polymethylmethacrylate (PMMA) bead chains has been used extensively in Europe for treatment of chronic osteomyelitis (14). More recently, the prophylactic use of tobramycin-impregnated PMMA beads has been reported in patients with open fractures (6,12). However, a second surgical procedure is often required for retrieval of the beads because the PMMA cement is a nonresorbable foreign body (15).

In 1984, Setterstrom et al. (23) reported the development of biodegradable ampicillin-loaded microspheres and their efficacy for the local treatment of contaminated soft-tissue wounds in rats. In this controlled-release delivery system, the antibiotic was microencapsulated in a copolymer of poly-(DL-lactide-co-glycolide) that gradually biodegrades to lactic acid and glycolic acid, which are normal metabolic products (5). As the copolymer is resorbed, the antibiotic is released in a sustained fashion over 21 days. Studies have shown that ampicillin microspheres were effective for the prevention of infection in contaminated open femoral fractures in rats (22) and for the local treatment of experimental staphylococcal osteomyelitis in rabbits (13). Recent efforts have led to the development of biodegradable cefazolin sodium microspheres. The objective of this study was to evaluate the efficacy of local therapy with cefazolin microspheres for the prevention of infection in rabbits with contaminated open tibial fractures stabilized with internal fixation.

MATERIALS AND METHODS

Cefazolin Microspheres

The cefazolin sodium microspheres (composite batch F468-101-1S; Southern Research Institute, Birmingham, AL, U.S.A.) consisted of 85.5 weight % copolymer (51:49 molar ratio of lactide to glycolide) with a core-loading dose of 14.5 weight % cefazolin sodium. The size of the microspheres ranged from 125-1,000 μm in diameter, and they were sterilized with 2.0 Mrad of gamma radiation. In vitro release-kinetic studies were performed by Southern Research Institute to measure the total amount of cefazolin released from the microspheres over time. A known amount of cefazolin microspheres was suspended in a receiving fluid of sodium phosphate buffer (pH 5.5), and the tube was maintained at 25°C for 14 days. At various intervals, the receiving fluid was decanted and was replaced with an equivalent volume of fresh sodium phosphate buffer. The samples were stored at 4°C until all specimens had been collected, and the amount of cefazolin released into the receiving fluid was measured by high-pressure liquid chromatography. In vitro release-kinetic studies indicated that approximately 20% of the cefazolin was released from the microspheres within the initial 24 h, and 91% was released over 14 days. Placebo microspheres (composite batch G100-096-01S) were prepared according to the same encapsulation process and conditions as for the cefazolin-loaded microspheres but without antibiotic.

Bacterial Inoculum

Staphylococcus aureus (27660; American Type Culture Collection [ATCC], Rockville, MD, U.S.A.) was used to contaminate the fractures. This strain is coagulase positive and produces penicillinase, and the minimum inhibitory concentration (MIC) of cefazolin was 2.0 μg/ml. The organism was grown in tryptic soy broth (TSB) at 37°C for 15 h and was diluted appropriately with TSB to yield a final concentration of 3.2×10^7 colony forming units (CFUs) per milliliter. The inoculum was frozen in 1 ml aliquots and was stored at −70°C. Quantitative bacterial counts were performed on each day of surgery and showed no significant reduction in viability.

Fracture-Fixation Model

A total of 32 New Zealand White male rabbits, weighing 2.7-3.3 kg each, were used. Of the 32, two animals died from the anesthesia before surgery, and another was given a lethal overdose intraoperatively because of a longitudinal split in the tibial cortex that could not be adequately stabilized. The animals were housed in individual cages and were fed a standard laboratory diet ad libidum. The exper-

TABLE 1. *Clinical and bacteriological findings*

Treatment group	No. of animals with deep infection	No. of animals with cultures positive for *S. aureus*	Mean (± SD) log bacterial counts (CFU/g)[a]
A: Cefazolin microspheres (n = 7)	0	1	0.3 ± 0.9
B: Free Ancef powder (n = 6)	0	1	0.2 ± 0.5
C: Systemic Ancef (n = 5)	3	4	3.0 ± 2.1
D: Control, placebo microspheres (n = 3)	3	3	5.2 ± 0.2
E: Control, no treatment (n = 4)	3	4	4.2 ± 0.5

[a] Mean log *S. aureus* counts for groups A and B are significantly different from all other groups by analysis of variance ($p < 0.05$). Group C is significantly different from all other groups ($p < 0.05$) except group E.

iments were conducted in accordance with established principles for the care and use of laboratory animals (4). The animals were anesthetized with a subcutaneous injection (0.5 ml/kg) of a solution containing (vol/vol) 55% ketamine hydrochloride, 28% xylazine, and 17% acepromazine maleate. The right hind leg was shaved and was sprayed with povidone iodine, and the surgical field was isolated with sterile drapes. The dermis and subcutaneous tissue along the anterior crest of the tibia were infiltrated with 2% lidocaine with epinephrine, and an incision was created down to the deep fascia and periosteum. The periosteum and the overlying musculature were split down the midportion of the bone, and the entire medial surface of the tibia was exposed. A four-hole plate was positioned on the tibia, and the proximal and distal screw-holes were drilled, tapped, and fixed with 2.7 mm cortical screws (10-14 mm long). After these screws were in place, the two middle screw-holes were prepared in the same fashion. The plate was then removed, and three additional holes were drilled in the bone between the two innermost screws. A bone biter was used to connect the three drill-holes; this resulted in a fracture in the middle of the shaft. The fracture then was displaced manually, and the site was inoculated with 0.5 ml of a freshly thawed *S. aureus* suspension. The bacteria were allowed to remain in the unreduced fracture site for 30 min before treatment was initiated.

After the delay, the animals were assigned to one of five groups. Group A (eight rabbits) received a local application of 300 mg of cefazolin sodium microspheres containing 43.5 mg of cefazolin equivalent. The cefazolin microspheres were sprinkled directly on the unreduced fracture site and over the deep surfaces of the periosteum and musculature. Group B (seven rabbits) received a local application of 45.6 mg of free cefazolin sodium powder (Ancef; SmithKline Beecham, Philadelphia, PA, U.S.A.) containing 43.5 mg of cefazolin equivalent. The antibiotic powder was applied to the fractures and the deep tissue in a manner similar to that for the microspheres. Group C (seven rabbits) received systemic Ancef (30 mg) subcutaneously every 8 h for 7 days, with the initial dose given 30 min after bacterial contamination. Group D (three rabbits) and group E (four rabbits) served as controls and received either a local application of 300 mg of placebo microspheres or no treatment, respectively.

The tibia was reduced and the plate applied, with the screw fixation being sequenced from proximal to distal. In 11 animals, a double loop of 3 × 10 mm stainless-steel wire was placed around the bone and the plate because plate fixation alone was deemed inadequate to achieve stability. Once the plate was in position, the animals in groups A and B received an additional local dose of either cefazolin microspheres (300 mg) or free Ancef powder (45.6 mg), respectively. These were applied directly to the fixation plates and the periosteal tissue just prior to primary closure of the wound. The animals in group D received an additional local dose of 300 mg of placebo microspheres. The periosteal tissue was then sutured over the plate with 4.0 Vicryl (Ethicon, Somerville, NJ, U.S.A.); the skin was closed with 4.0 Prolene (Ethicon). Each animal received three doses (1 mg each) of butorphanol tartrate (Torbugesic; Fort Dodge Laboratories, Fort Dodge, IA, U.S.A.) subcutaneously at 8 h intervals for routine control of postoperative pain; additional doses were given, if necessary, on the basis of clinical symptoms. The animals in groups A and B were bled via the ear for quantitation of serum cefazolin at 1 and 24 h after local application of either cefazolin microspheres or free Ancef powder. The serum concentrations of cefazolin were measured by an agar diffusion technique previously described by Bennett et al. (1). The animals were returned to their cages and were monitored daily over the

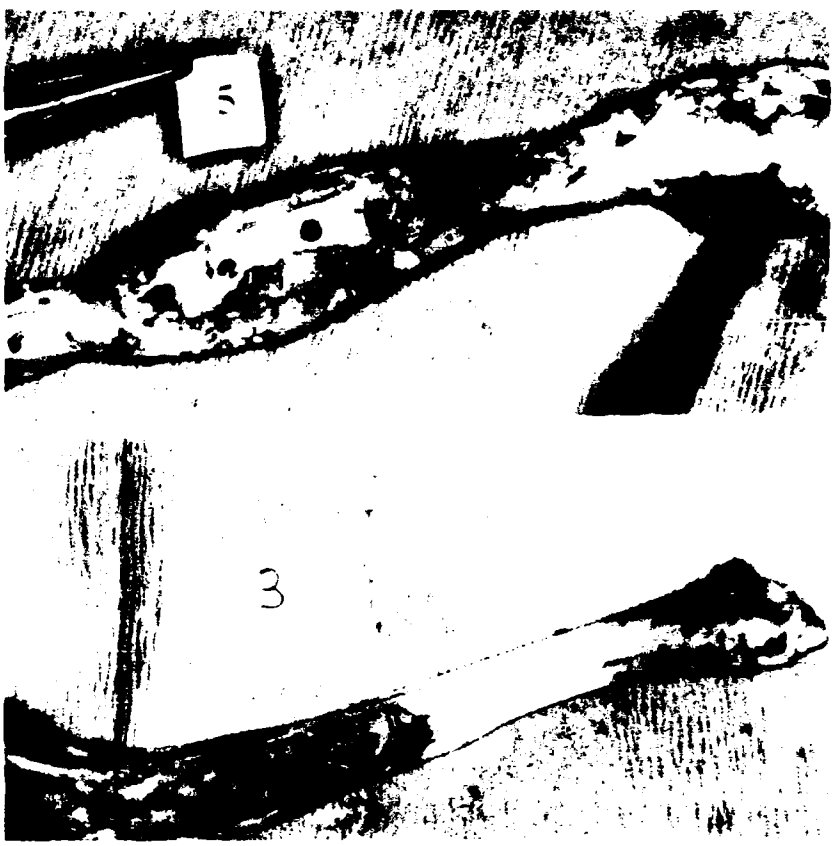

FIG. 1. Top: Tibia from a control rabbit in group D (placebo microspheres) with culture-positive osteomyelitis, showing extensive callus formation and disorganized bone growth. Bottom: Tibia from an animal in group A (cefazolin sodium microspheres), showing normal fracture healing without clinical evidence of infection.

FIG. 2. Tibia from an animal in group B (local free Ancef powder), showing periosteal new bone formation on the distal segment of the plate.

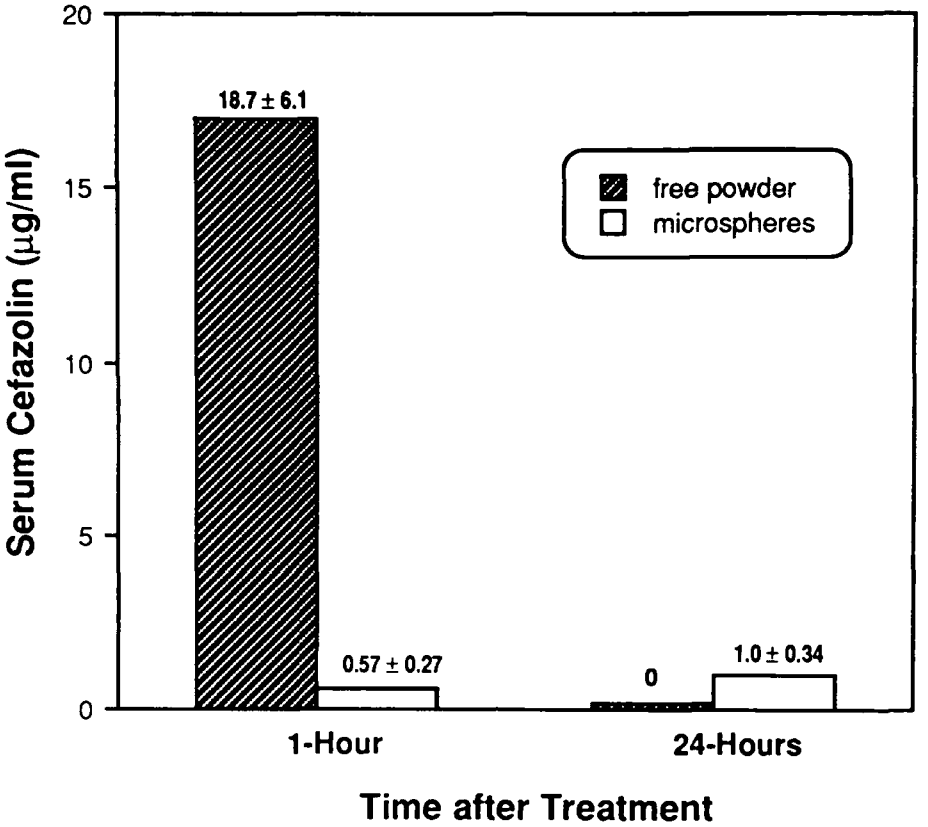

FIG. 3. Serum concentrations of cefazolin at 1 and 24 h in rabbits treated locally with either cefazolin sodium microspheres (group A) or free Ancef powder (group B).

next 8 weeks for clinical signs of wound infection.

Cultures of Bone

All surviving animals were given a lethal overdose at 8 weeks by intracardiac injection of sodium pentobarbitol, following induction of anesthesia with ketamine and xylazine. The tibiae were harvested aseptically, and the plates and screws were removed and placed in a tube containing 10 ml of TSB. The tibiae then were crushed to small pieces with a sterile mortar and pestle, and 10 ml of saline solution was added to make a particulate suspension. Serial dilutions of this suspension were prepared in normal saline solution, and 100 µl of each dilution was streaked on blood agar plates. The number of *S. aureus* colonies recovered from each specimen was quantitated and expressed as CFU/g of bone.

RESULTS

Three animals (one each from groups A, B, and C) sustained another fracture of the tibia within 24 h after plating and were immediately killed. Of these three animals, cultures of the tibiae from those that had received local antibiotic therapy with either cefazolin sodium microspheres (group A) or free Ancef powder (group B) showed no growth. No material was taken for culture from the animal in group C, as this rabbit had received less than one full day of therapy with systemic Ancef. Another animal in group C sustained a repeat fracture after receiving subcutaneous injections of Ancef for 3 days and died of associated hemorrhage. High concentrations of *S. aureus* (2.71×10^5 CFU/g) were recovered from the tibia of this animal. Of the 29 rabbits that had had osteotomy, bacterial contamination, and plate fixation, 25 (86%) survived the 8 week experimental protocol. All surviving animals tolerated the surgical procedure well and were able to ambulate freely in their cages within a week after fixation of the fracture. No abscess, purulent drainage, or other clinical evidence of wound infection was noted in any of the involved limbs.

Although all of the fractures appeared to be solidly united when the animals were killed, as de-

termined by subjective manual testing of the disarticulated tibiae, the callus was grossly enlarged in six of the seven control animals that had received either local placebo microspheres (group D) or no treatment (group E). Table 1 shows the results of the clinical and bacteriological findings. Deep infection, as evidenced by the presence of pus on the plates and in the deep tissue, was noted in all three animals in group D and in three of the four animals in group E. *S. aureus* was grown on culture of material from the fixation plates as well as from the tibiae of all seven control animals. In contrast, no clinical evidence of infection was noted in any of the seven surviving animals in group A (local treatment with cefazolin microspheres) or in the six animals in group B (local treatment with free Ancef powder). Macroscopically, the tibiae of all of these animals appeared to be solidly united, and the callus was only slightly enlarged compared with that of the controls (Fig. 1). In several cases, periosteal new bone formation covered a segment of the plate (Fig. 2). Cultures of material from the fixation plates and the tibiae showed no growth in six (86%) of the seven animals in group A and in five (83%) of the six animals in group B. In contrast, of the five surviving animals in group C (systemic Ancef), deep infection was present in three and *S. aureus* was grown on culture of material from the tibiae of four.

Figure 3 shows the mean serum concentrations of cefazolin that were detected at 1 and 24 h following local treatment with either cefazolin microspheres or free Ancef powder. The mean serum levels of cefazolin at 1 h were significantly higher for the animals in group B (free Ancef powder) (18.7 ± 6.1 μg/ml) than for the animals in group A (cefazolin microspheres) (0.57 ± 0.27 μg/ml). Although the serum levels of cefazolin had returned to baseline after 24 h in the animals in group B, a mean serum cefazolin concentration of 1.0 ± 0.34 μg/ml was measured for the animals in group A.

DISCUSSION

A previous study by Burke (2) involving cutaneous lesions in guinea pigs indicated that there was a definitive period of time during which bacteria were most susceptible to prophylactic systemic antibiotics. Burke demonstrated that staphylococcal wound infection could be prevented if the antibiotic was given before bacterial contamination; however, a beneficial effect was noted even when antibiotic therapy was delayed for as long as 3 h. Similarly, Patzakis et al. (17) noted a significant reduction in the incidence of clostridial myonecrosis when rats with an experimental tibial fracture received systemic penicillin, even when treatment was delayed for 3 h after bacterial inoculation. However, neither of these studies involved contaminated wounds in which a foreign body also was present. Although, in the current study, systemic antibiotic therapy for the animals in group C was initiated 30 min after contamination of the fractures, post-traumatic osteomyelitis developed in 60% of these animals. Rethman et al. (22) and Worlock et al. (29) also reported that systemic antibiotic therapy, initiated within a few minutes to 1 h after bacterial contamination, failed to prevent infection in most rats (22) and rabbits (29) with experimental open fractures stabilized with internal fixation. These combined results suggest that the effective period of systemic prophylactic antibiotics is considerably shorter in the presence of internal fixation than the effective time of 3 h that has been reported for contaminated wounds without a foreign body (2,17). This is not totally surprising, in light of the fact that many commonly used orthopaedic implant materials have been shown to be infection-potentiating factors in animal models (21). It also has been postulated that bacterial adherence to foreign bodies, with subsequent production of a thick glycocalyx biofilm may act as a barrier to the diffusion of antibiotics (7), that may account, in part, for the high rate of infection noted with systemic Ancef therapy in the present investigation.

In contrast to the poor results achieved with systemic antibiotic therapy in this study, single-dose local treatment with either cefazolin microspheres or free Ancef powder was highly effective for preventing the onset of infection with *S. aureus*. Perhaps the most surprising finding was that the free antibiotic powder was as effective as the cefazolin microspheres that were formulated for sustained release of the antibiotic over 2 weeks. Two previous studies reported the efficacy of local therapy with cephalosporin antibiotics in experimental wounds. Waterman et al. (27) noted a significant reduction in the incidence of infection in guinea pigs with experimental soft-tissue wounds that had been contaminated with *S. aureus* and treated, within 1 h, by local deposition of cephalothin powder. In a similar study, Stringel et al. (25) reported that local application of cefamandole powder to thigh-muscle wounds in rats, 30 min after bacterial contamination, was signifi-

cantly more effective than systemic administration for the prevention of infection with *S. aureus*, *E. coli*, and *B. fragilis*. It should be emphasized, however, that both of these studies evaluated local antibiotic therapy in contaminated soft-tissue wounds without a foreign body. One significant finding of the present study, therefore, is that it expands the previously reported beneficial effects of locally applied cephalosporin antibiotics to include contaminated open fractures stabilized immediately with internal fixation. The excellent clinical and bacteriological results obtained with local antibiotic therapy compared with systemic Ancef therapy in this fracture-fixation model was most likely due to the significantly higher antibiotic concentrations that were achieved locally at the fracture site. Although we did not measure tissue or bone concentrations of cefazolin, previous studies have shown that high concentrations in local tissue can be achieved following application of free antibiotic powder to experimental wounds (25,27). Whereas high local levels can be maintained for only about 24 h after local application of free antibiotic powder, Setterstrom et al. (23) measured antibiotic concentrations in tissue that were significantly more than the MIC for *S. aureus* even at 1 week after local application of ampicillin-loaded microspheres to contaminated soft-tissue wounds in rats.

On the basis of the dramatic results noted in this study with free antibiotic powder, the question arises as to what benefits, if any, may be offered by the microencapsulated formulation. One major advantage is that the microspheres can be given in a single dose and formulated for sustained release of the antibiotic for a period ranging from a few days to several weeks. A controlled-release delivery system, which can provide high local concentrations of antibiotic for an extended time, would be not only advantageous, but indeed necessary, for the treatment of chronic bacterial infections. This observation is supported by our previous study on the efficacy of local antibiotic therapy for the treatment of experimental staphylococcal osteomyelitis in rabbits (13). In that study, a single intramedullary application of ampicillin microspheres, which released the drug over 3 weeks, sterilized the tibiae of all 10 animals when treatment was delayed for 7 days. In contrast, of the 10 rabbits that received local therapy with an equivalent dose of free ampicillin powder, culture-positive osteomyelitis developed in 70%. These combined results suggest that free antibiotic may be beneficial if applied to an open fracture wound shortly after bacterial contamination; however, its efficacy would be significantly reduced if treatment were delayed and the bacteria had become established in the wound site. Although the average time from injury to definitive surgical treatment for open fracture wounds at one major trauma-designated hospital has been estimated to be 3.2 h (11), this can vary significantly among institutions. For example, in a study of 1,104 open fractures treated at Los Angeles County—University of Southern California Medical Center, Patzakis and Wilkins (19) reported that definitive surgical debridement in the operating suite was delayed for 12 h or longer in 64% of the cases. As noted by Gustilo (11), if surgical treatment of an open fracture is delayed 8 h or more, the wound should be considered infected rather than contaminated. Under these circumstances, it is reasonable to assume that a controlled-release antibiotic formulation would be more effective than free antibiotic powder because of the former's ability to provide and maintain high antibiotic concentrations at the wound site for a prolonged time.

A second advantage offered by antibiotic-loaded microspheres is that the potential for adverse systemic side effects is minimized. As shown in Fig. 3, significantly higher mean serum concentrations of cefazolin were detected at 1 hr in the animals that had local application of free Ancef powder than in the animals treated with cefazolin microspheres. Although high systemic levels of antibiotic are of less concern with some antimicrobial agents, with others, particularly the aminoglycosides, the potential for nephrotoxicity and ototoxicity is an argument against the use of free antibiotic powder in open wounds and fractures, especially in patients who have impaired renal function. In fact, the previously widespread practice of the use of a neomycin lavage solution after total hip arthroplasty has been discontinued because of a reported high incidence of toxicity (28). The toxicity associated with the aminoglycosides can be minimized, however, by encapsulation of the antibiotics in a controlled-release polymer. This observation is based on our preliminary results with amikacin-loaded microspheres in animals (unpublished data), as well as on the vast clinical experience with the use of gentamicin-impregnated PMMA beads in patients.

In conclusion, the results of the present investigation, in conjunction with the findings from our previous studies (13,22,23), indicate that antibiotic-loaded microspheres are highly effective for the lo-

cal treatment of contaminated soft-tissue and open fracture wounds even in the presence of a foreign body. The development of biodegradable controlled-release antibiotic microspheres represents a major advance in drug delivery systems with considerable clinical potential for the management of contaminated or infected surgical and traumatic wounds. Poly-(DL-lactide-co-glycolide) is an ideal polymeric excipient for in vivo drug delivery, primarily because it is nontoxic and is resorbed completely to carbon dioxide and water. Although microencapsulated antibiotics currently are not available for use in humans, the fact that resorbable sutures fabricated with lactide and glycolide have been in clinical use for more than a decade should facilitate the regulatory approval process for this novel antibiotic delivery system.

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